Uterine corpus cancers, the vast majority of which are endometrial carcinomas, are diagnosed in approximately 47,130 women every year in the United States, which makes them the most frequently diagnosed malignancy of the gynecologic tract, and the 4th most commonly diagnosed malignancy in women overall [1]. The vast majority of endometrial carcinomas are of the endometrioid histotype, are localized to the uterus at presentation, and accordingly have a good prognosis [2]. Endometrial serous carcinomas (ESC), also known as uterine papillary serous carcinomas, represent about 10% of endometrial carcinomas, and have traditionally been conceptualized as being a clinically aggressive histotype [3, 4] since they are responsible for up to 40% of all deaths and recurrences associated with endometrial cancer [5]. At the clinical level, this aggressiveness is related, at least partially, to the comparatively higher stage at which ESC patients present [2]. Endometrial serous carcinomas (ESC), also known as uterine papillary serous carcinomas, represent about 10% of endometrial carcinomas, and have traditionally been conceptualized as being a clinically aggressive histotype [3, 4] since they are responsible for up to 40% of all deaths and recurrences associated with endometrial cancer [5]. At the clinical level, this aggressiveness is related, at least partially, to the comparatively higher stage at which ESC patients present [2]. For example, amongst the endometrial cancers reported to the International Federation of Gynecology and Obstetrics for the 1999-2001 period, only 1021 (13.9%) of the 7333 endometrioid cancers were late stage, as compared with 143 (41.3%) of 346 ESCs [2]. At least 37% of ESC cases that display no invasion in the uterus are found to have stage III or IV disease after comprehensive surgical staging, which highlights the significance of the latter procedure in accurately defining the extent of disease for patients with this cancer [6]. However, for patients that truly have uterine corpus-confined disease after surgical staging, and certainly those with stage IA, non-myoinvasive or minimally-invasive disease, the reported outcomes have been good to excellent [7-15], although the optimal adjuvant management for these patients remains a matter of debate [16, 17]. For patients with stage III or IV disease, reported outcomes have generally been dismal, irrespective of adjuvant therapeutic modalities [18, 19]. These findings highlight the importance of intercepting the disease at an early stage, and possibly applying an ablative intervention before its development [20, 21].

The concept of an intraepithelial, non-invasive, and possibly precancerous phase of ESC has been recognized for nearly two decades. This lesion has variably been designated as “endometrial intraepithelial carcinoma” (EIC), “serous EIC”, “uterine surface carcinoma”, “endometrial carcinoma in situ” and “minimal serous carcinoma” [22-27]. This lesion is characterized by the colonization and replacement of benign surface endometrium and glands by cells that are cytologically identical to serous carcinoma, is frequently multifocal, is seen in association with up to 89% of ESC cases, and was postulated to represent the precursor lesion to ESC for many years [28]. It has also long been recognized, however, that a significant
subset (up to two-thirds) of patients with pure serous EIC (and no ESC as conventionally defined) may have extraterine disease of the same morphology, immunophenotype, and molecular features [29-32]. The specific biologic properties of carcinomas with the serous phenotype (possibly related to alterations in cell adhesion molecules) confers upon them the ability to disseminate even in the absence of a morphologically apparent invasive growth. Therefore, as a practical matter, although serous EIC may represent a non-invasive appearing growth pattern of ESC, it has the same clinical implications as the latter, and cannot be considered a precancerous lesion for the purposes of prevention. This recognition is reflected in the patient management recommendations for serous EIC, which largely mirror those for early stage conventional ESC, and include total hysterectomy, bilateral salpingo-oophorectomy, pelvic and periaortic lymph node dissections, multiple peritoneal biopsies and omentectomy, with the need for adjuvant chemotherapy being dependent on the resultant findings [32].

Studies from our group over the past decade have defined a lesion that we consider to be a more likely preccancer for ESC, and which we have defined as “Endometrial glandular dysplasia” (EmGD) [33-38]. In one study, this lesion was identified in approximately half (53%) the “benign” endometria adjacent to the conventional ESC cases that were examined, as compared with 1.7% of the endometrioid cancers [34]. The typical EmGD focus shows epithelial segments (surface epithelium or isolated single cells) lined by cells with nucleomegaly (2-4 times resting endometrium, as compared with 4 -5 times in serous EIC), appreciable but non-conspicuous nucleoli, variable hyperchromasia, loss of nuclear polarity, and generally stand out from the background endometrium in which they are identified. They are multifocal in up to 86% of patients, but each focus is usually less than 1 mm [20]. We have recently outlined the evidentiary basis for the consideration of EmGD as the precancerous lesion for ESC in a recent authoritative review article [20]. EmGD fulfills the National Cancer Institute criteria for a precancerous lesion [39], as briefly summarized below. The first criterion calls for the putative precancerous lesion to be distinct from the normal tissue from which it arose. As outlined above, EmGD fulfills this criterion. The second criterion calls for the putative precancer to share some, but not all molecular and phenotypic properties of the cancerous lesion. As we have detailed elsewhere, when the TP53 mutational load between ESC (including serous EIC) and EmGD were compared, it is clearly greater in the former [20]. At the morphologic level, by definition, ESC/EIC displays greater anaplasia than EmGD. At the phenotypic level, insulin-like growth factor II mRNA-binding protein 3 (IMP3), a protein that is highly expressed in ESC, shows a significantly lower expression level in EmGD as compared with ESC [36]. The third criterion that must be fulfilled is that when a precancer progresses to cancer, the resulting cancer must arise from cells within the precancer. Our analysis of TP53 gene mutations (exons 5-8) in 6 uteri with EmGD and ESC identified at least 1 identical mutation in all six [20]. HUMARA assays have also identified identical allele losses in synchronous lesions of EmGD, serous EIC and ESC in up to 75% of cases [20]. The fourth criterion is that there is a method by which the precancerous lesion can be diagnosed (see diagnostic morphologic features above). The fifth and final criterion is that the precancerous lesion increases the risk for cancer. On the latter point, there is only one retrospective study available, in which the “benign” biopsies that preceded the diagnosis of ESC were re-evaluated and lesions meeting the diagnostic criteria for EmGD were re-analysed [35]. On the basis of this study, it was estimated that the diagnosis of EmGD in an endometrial biopsy may confer up to a 9-fold increased risk for developing ESC, although it is readily acknowledged that additional research is warranted to truly define the natural history of the lesion [35]. Accordingly, based on the totality of these clinicopathologic findings, EmGD is the most likely candidate precancer for ESC at present time.

A variety of molecular alterations have been described in ESC. The primary molecular event involves mutations in the TP53 tumor suppressor gene, which appears to be an early event in serous carcinogenesis and a frequent, near-uniform event in the established malignancy. TP53 gene mutations occur in 22.7 to 96% of ESC, and p53 protein overexpression is seen in approximately 76%-90% [21]. Morphologically normal endometrial cells adjacent to ESC have been found to occasionally display strong p53 expression as assessed by immunohistochemistry, and these foci have been designated as “p53 signatures” [38, 40]. P53 signatures have
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a significantly stronger association with serous, as compared with endometrioid carcinomas, and have a frequency of TP53 gene mutations that is comparable to EmGD, but significantly less than serous EIC/ESC (38). Furthermore, occasional cases show identical TP53 mutations in all 3 lesions (p53 signatures, EmGD, serous EIC/ESC). These, and other findings formed the basis for a model of endometrial serous carcinogenesis that we have recently proposed, in which a sequence of lesions appear through the progressive accumulation of molecular aberrations: resting endometrium → p53 signatures → EmGD → serous EIC → ESC [20]. Other noteworthy molecular and phenotypic aberrations that have been described in ESC include genetic instability, the upregulation of p16 and the probable dysregulation of both the p16(INK4a)/Cyclin D-CDK/pRb-E2F and the ARF-MDM2-p53 cell cycle pathways, HER2/neu amplification, PIK3CA mutations, overexpression of IMP3, EGFR, HMG2 and Nrf2, the loss of expression of CD44 and the estrogen and progesterone receptors, evidence of epithelial-to-mesenchymal transformation, and alterations in the expression of cell-adhesion molecules [20, 21, 41-47]. As previously noted, TP53 mutations appear to be the central and earliest molecular events in endometrial serous carcinogenesis [20, 21].

As is true with many cancers, a significant reduction in patient mortality can be achieved by the diagnosis and treatment of the disease at an early stage once it develops, or prevention of the disease from developing in the first place. The accurate diagnosis and treatment of the precursor lesions for ESC is one preventive approach that may ultimately reduce the incidence and mortality of this disease. At present, irrespective of whether a patient is at the EmGD, serous EIC or ESC phase of their disease, an endometrial biopsy needs to be performed, usually due to the patient’s presentation with abnormal uterine bleeding or abnormal glandular cells found on Pap smears. Unfortunately, there are presently no non-invasive screening methods that have been shown to be effective for endometrial carcinomas in general. Given the central role that TP53 mutations play in endometrial serous carcinogenesis, one possibility, which we are currently in the process of evaluating, is the utility of serum anti-p53 antibodies in this setting. In lung and head and neck cancers, there are reports that not only variably ascribe some prognostic value to the assessment of these antibodies, but also suggest that anti-p53 antibodies may be seen in the subclinical phase of cancer development [48-51]. It would therefore be of tremendous interest to investigate how early anti-p53 antibodies are detectable in the process of ESC-development, and whether their measurement will provide the requisite level of sensitivity and specificity for clinical use, including the stratification of patients with a biopsy diagnosis of EmGD regarding their risk of a concurrent more serious lesion. Large scale, multi-institutional studies are urgently needed to prospectively define the outcomes in patients that are diagnosed with a serous precancer (or a lesion that is suspicious for a precancer) in an endometrial biopsy. Evidence-based patient management guidelines can then be formulated and uniformly applied. Meanwhile, we can only hope that with continued research and resultant clarification of these issues, the promise of a preventive approach will move out of the theoretical realm into the practical one.

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